REMARKS

Claims 42-47, 49-54, 56-57, 82-85, 90, 92, 94, 96, 100 and 102-103 are pending for examination with claims 42, 44, 82, 90, 92, 94 and 96 being independent claims. The specification has been amended to correct the address for the ATCC, as suggested by the Examiner. No new matter has been added.

Summary of Telephone Conference with Examiner

Applicants thank Examiners Minnifield, Nelson, and Smith for conducting a telephone interview with the undersigned Applicants' representative and Mark Nelligan, Esq. (representative for a licensee) on February 9, 2005.

During the interview the issue of enablement of the claims was discussed. In particular Applicants indicated places in the specification that described support for the use of CpG alone (without the concurrent administration of an allergen). The Examiners indicated that it would be helpful for Applicants to submit evidence demonstrating that the experimental model described in Example 12 was a model for the treatment of asthma, that CpG had been administered safely to humans and any data relating to the use of CpG for the treatment of asthma. Applicants enclose herewith this information.

Objection to Information Disclosure Statement (IDS)

The Examiner has indicated that some of the references cited on the August 27, 2004 IDS have not been considered. The Examiner requests that Applicants submit copies of the references cited in that IDS which were not initialed by the Examiner.

Applicants assert that copies of all of the indicated references were mailed to the US Patent Office with the August 27, 2004 IDS. In order to advance prosecution Applicants submitted, on April 8, 2005, another copy of the references and 1449. Applicants respectfully request that the Examiner consider each of the references and return an initialed copy of the 1449 to Applicants.

The Examiner has also returned copies of the 1449 forms filed with other IDSs. On those 1449 forms the Examiner has initialed a few references and signed the bottom of each page and struck out a few references. In order to clarify the status of these references, Applicants'

representative called the Examiner on March 21, 2005 and discussed the forms. According to the Examiner, the references without her signature were not scanned into the system and thus not accessed by her. The Examiner suggested contacting the Help Desk or OIPA to discuss the best way for resolving the issue. The OIPA never answered several calls. On April 6, 2005, Helen Lockhart was informed by Ray of the Help Desk that Applicants should submit duplicate copies of the references directly to the Examiner in order to avoid the afore-mentioned problem.

Applicants wish to point out on the record that copies of the references were provided with a 1449 form and IDS. Thus Applicants have met the requirements of 37 CFR 1.98. In order to expedite prosecution, Applicants have filed on April 8, 2005 a clean copy of the 1449 form listing all of those references not initialed by the Examiner and additional copies of the references that the Examiner has indicated were missing. Out of an abundance of caution, Applicants are also following the advice of the Help Desk and have submitted a copy of the 1449 form and references directly to the Examiner. It is respectfully requested that the Examiner consider the remaining information presented in the IDS prior to taking any further action on the merits and to return a copy of the initialed 1449 form to Applicants.

Rejections under 35 U.S.C. §112

The Examiner rejected claims 42-47, 49-54, 56-57, 82-85, 90, 92, 94, 96, 100 and 102-103 under 35 U.S.C. §112 for a lack of enablement.

The Examiner has indicated that a method for treating asthma using SEQ ID NO. 10 is enabled but that the use of other CpG containing oligonucleotides is not enabled. Applicants respectfully disagree.

Applicants have described a class of molecules (oligonucleotides) having a common structural motif (a CpG dinucleotide) that when administered to a subject result in an aspect of the immune response being altered, with a Th1 response being favored. This class of oligonucleotides are described throughout the specification and their ability to produce a Th1 favored immune response is not only described (e.g., see page 8, lines 22-23 and 25-27, page 9, lines 8-9 and page 53, line 26 – page 54, line 5) but data is presented in vitro and in vivo using a number of different CpG containing oligonucleotides. For instance, Table 5 shows induction of Th1 cytokines using several different oligonucleotides.

In addition to the working examples a number of studies published since the filing of the patent application have reiterated, as set forth in the specification, that CpG oligonucleotides having different structures but maintaining the critical CpG motif result in an altered immune response. For instance, US Patent Application Serial No. 10/644,052 corresponding to PCT Publication No WO2004/016805 (copy enclosed as exhibit 4) describes numerous examples of CpG oligonucleotides that stimulate an immune response. The application includes 10 Tables and 39 Figures of data.

It is now believed that CpG oligonucleotides act through a common cellular receptor, TLR9. It is believed that CpG oligonucleotides are recognized by TLR9 and that this leads to the promotion of an immune response in which a Th1 response is favored. Hemmi et al., Nature, 2002, vol. 408, page 740 was one of the first publications to describe the role of TLR9 in activation of the immune response by CpG oligonucleotides. A copy of the reference is attached for the Examiner with the IDS filed herewith. Briefly, Hemmi et al. describes studies in a TLR9 knockout mouse. The CpG mediated Th1 immune response was abolished in these mice, confirming the role of TLR9 in CpG mediated signaling.

The Examiner has also indicated that a method for treating asthma using a CpG containing oligonucleotide with an allergen is enabled but that use without an allergen is not enabled. Applicants respectfully disagree.

The above-identified patent application is based on the discovery that a class of molecules that include a CpG motif promote a very specific and effective immune response. The immune response includes activation of the adaptive as well as the innate immune systems. As it relates to the adaptive immune system it is useful in combination with an antigen to promote an antigen specific immune response. However, as described in the specification, CpG oligonucleotides were shown to promote NK cell activation (not an antigen specific immune cell) as well as to alter profiles of cytokines, independent of antigen administration. The specification describes the use of CpG for therapeutic purposes based on this discovery.

The application includes 14 Tables of data in addition to the data presented in the examples section of the patent application, which itself includes 15 Figures of data. The majority of this data is conducted using CpG oligonucleotides either in vitro or in vivo without the concurrent use or administration of an antigen.

The methods for treating asthma are described throughout the application in terms of the administration of CpG as a therapeutic. It is taught that an immune profile which is consistent with the promotion of a Th1 favored response is important in asthma. The experimental work examining shifts in cytokine induction were achieved using CpG alone without an allergen. For instance, CpG oligonucleotides were used alone without antigen/allergen to produce Th1 biased cytokine induction in Table 5 and Table 13. No antigen was administered. Th1 cytokines include IFN-γ, TNF-α, IL12, and GM-CSF.

Example 12 is an in vivo study using an animal model to demonstrate the efficacy of CpG oligonucleotides in the treatment of asthma. In the interview, the Examiner questioned the acceptance of the model used in Example 12 as a model for the treatment of asthma and asked Applicant to provide a publication describing this model. Attached hereto are 3 publications describing the use of airway inflammation induced by schistosome egg antigen in vivo as a model of asthma. These papers include: *Lukacs NW, et al., Interleukin-4-dependent pulmonary eosinophil infiltration in a murine model of asthma. Am J Respir Cell Mol Biol. 1994 May;10(5):526-32; Padrid PA, et al., CTLA4Ig inhibits airway eosinophilia and hyperresponsiveness by regulating the development of Th1/Th2 subsets in a murine model of asthma. Am J Respir Cell Mol Biol. 1998 Apr;18(4):453-62*; and *Lukacs NW, et al., C-C chemokine-induced eosinophil chemotaxis during allergic airway inflammation. J Leukoc Biol. 1996 Nov;60(5):573-8.* (copies enclosed with IDS filed April 8, 2005 and as Exhibits 1-3).

Lukacs et al. 1994 reports that schistosome egg antigen induces a Th2 response in mice, and elicits an inflammatory reaction in lungs. Histologic examination of the lungs demonstrated a characteristic influx of eosinophils. Examination of interleukin-4 (IL-4) production in the airway fluid demonstrated the presence of IL-4 early in the response. Mice treated with anti-IL-4 antibodies demonstrated a tenfold decrease in airway eosinophil influx. This data demonstrates that the eosinophilia induced by schistosome egg antigen is dependant on a Th2-type (IL-4) response.

Padrid et al. reports that blockade of T cell stimulation blocks airways inflammation induced by schistosome egg antigen. This blockade resulted in decreased antigen-induced airway eosinophilia and antigen-induced reduced Th2 cytokine (interleukin-4 and interleukin-5)

secretion in airways. The authors conclude that the suppressed eosinophilia is most likely due to attenuated secretion of Th2-type cytokines.

Lukacs et al. 1996 demonstrated the production of eosinophil-specific chemotactic factors during allergic airway responses to schistosome egg antigen.

As demonstrated in the cited publications, airway inflammation induced by schistosome egg antigen is a recognized mouse model of the allergic airway inflammation that is characteristic of asthma. Schistosome egg antigen induces a Th2-type response (i.e., secretion of Th2 cytokines from T cells) and an influx of eosinophils and other inflammatory cells into mouse lungs. Therefore, the model is suitable for investigating the effects of test compounds that suppress the effects of Th2 T cells (e.g., CpG oligonucleotides).

In Example 12, it is necessary to administer the schistosome eggs to the animal to create the airway inflammation characteristic of asthma. In this particular experiment the CpG is given at the same time as an allergen. It may be administered at different times as well. Nothing in Example 12 suggests that the use of CpG oligonucleotides alone as therapy for asthma does not work.

For instance, the data presented in US Patent Application Serial No. 10/644,052 corresponding to PCT Publication No WO2004/016805 (copy enclosed as exhibit 4) demonstrate that when CpG oligonucleotides are administered alone (not in conjunction with an allergen) the CpG oligonucleotides are effective in treating the asthmatic response. For instance, Examples 22 and 25-26 describe in vivo administration of a CpG oligonucleotide followed by assessment of cytokine profiles, eosinophil numbers (eosinophil volume density) and mucus secretion in lung tissue (determined by histopathological assessment).

Example 22 involves an assessment of the expression of cytokines in mouse lungs after administration to the airways, either by intranasal instillation or by bolus intravenous injection. An antigen was not administered. The CpG oligonucleotide induced expression of IL-6, TNFα, IFNα, IFNγ and IP-10 genes in the lung.

In Example 25 the effects of CpG oligonucleotides against antigen-induced airway inflammation in mice *in vivo* was assessed. Mice were initially sensitized on study days 0 and 7 with antigen (ovalbumin, 100 μg, i.p.) with aluminum hydroxide adjuvant and then challenged with antigen by exposure to inhaled ovalbumin aerosol, twice each week for two consecutive

weeks. CpG oligonucleotide or vehicle (saline) were administered into the airways by intranasal instillation once each week, two days before the first antigen challenge of the week. Endpoints were assessed 48 hours after the last antigen challenge. A summary of the study protocol is shown in Table 13. The results demonstrated that antigen challenge caused an increase in the total number of leukocytes, predominantly eosinophils, in the airway lumen and an accumulation of $CD4^+$ T cells ($CD3^+CD4^+$ cells). The eosinophilia and accumulation of $CD4^+$ T cells, however, was suppressed significantly in a dose-related manner by administration of CpG oligonucleotide. CpG oligonucleotide also significantly suppressed antigen-induced eosinophil accumulation in lung tissue and epithelial mucus secretion.

Example 26 demonstrated the effects of CpG oligonucleotides against antigen-induced airway hyperreactivity in mice *in vivo*. Mice were sensitized on study days 0 and 7 with antigen (ovalbumin, 100 μg, i.p.) with aluminum hydroxide adjuvant and challenged by exposure to inhaled ovalbumin aerosol, twice each week for two consecutive weeks. CpG oligonucleotides were administered intranasally once each week, two days before the first antigen challenge of the week. Airway hyperreactivity was assessed 24 hours after the last antigen challenge by measuring bronchoconstriction (increase in airway resistance) to intravenous methacholine. The study protocol is shown in Table 14. The data demonstrated that antigen challenge caused airway hyperreactivity. CpG oligonucleotide suppressed the development of antigen-induced airway hyperreactivity in a dose-related manner.

An important aspect of Example 12 of the instant patent application is that the CpG is acting as the therapeutic in the study. It is the CpG not the schistosome eggs that is producing this Th1 favored immune response. As shown in the data described above when schistosome eggs are administered to an animal in the absence of CpG oligonucleotides, a Th2 biased response and eosinophil influx occur. When the CpG oligonucleotide is administered to an animal primed for an asthmatic response, as is demonstrated in Example 12, a Th1 biased response is induced and eosinophil influx is inhibited.

The Examiner has cited several papers in support of the lack of enablement rejection. One of those papers, Jain & Kline provides a good description of the effects of CpG in the asthmatic airway. For instance page 1534, first column lines 7-13 teach "Preclinical studies have demonstrated the effectiveness of CpG oligonucleotides (ODNs) in the prevention and treatment

of both upper and lower allergic airway disease [7-11]. Data from ongoing human trials using CpG ODNs suggest that it is a safe and well-tolerated agent that seems promising for the treatment of allergic airway inflammation." Also, page 1536, first column lines 33-43 teach "Mice that received immunotherapy with CpG ODNs alone, as well as CpG ODNs along with allergen, prior to receiving RAE, had significantly inhibited development of GC hyperplasia and AHR. In those studies, the authors also characterised the epithelial changes by morphometric analyses and found that CpG ODNs also inhibit the amount of stored mucin in airway cells. Increased amounts of stored mucin (and subsequent GC degranulation) contribute to the pathogenic mechanisms for patients with asthma, including airway narrowing, exacerbations and accelerated decline in lung function."

Two references were cited in order to demonstrate that CpG was associated with dangerous side effects. The Satoh et al. reference is an abstract describing a study in which CpG oligonucleotides are administered subcutaneously to mice in combination with DNFB treatment and looking at T cell mediated hypersensitivity responses. The other reference cited for this proposition, Wohleben, provides a favorable view of CpG oligonucleotides and its usefulness in the treatment of asthma. It is touted as the most promising of approaches in the abstract. Even the cited paragraph on page 620 relates to the expectation that CpG oligonucleotides will be effective in humans.

Several Phase I and II studies have been performed in humans to date. In particular subcutaneous administration, like that in the Satoh reference, has been performed in humans for a cancer trial. The data are described in Kim et al., Blood, volume 4, issue 11, abstract # 743, Nov. 16, 2004 (copies enclosed with attached IDS and as Exhibit 5). Toxic effects that would halt further human trials were not observed, even though the patients were provided CpG oligonucleotides in very aggressive doses. The abstract concludes that "weekly doses up to 0.36 mg/kg have been well tolerated."

Weiner et al. is cited for the proposition that the molecular mechanism of CpG is unknown. It is generally believed in the field that CpG oligonucleotides are acting through TLR9. Regardless, knowledge of the mechanism isn't necessary.

Krieg and Kline (2000), Immunoph., 48, 303-305 (previously submitted to Patent Office in IDS) further teaches that CpG administered alone or at the same time as allergen is effective to

downregulate an airway inflammatory response. For instance, see page 304 second column first full paragraph which teaches "Further studies demonstrated that immunotherapy of established Th2-like airway responses can be effective using CpG DNA given SC, either together with or without allergen. The Th1-like environment induced by CpG DNA is sufficient to downregulate the subsequent inflammatory response to airways inhalation." These studies are consistent with the teachings of the instant patent application and the claimed invention.

The instant patent application includes a significant amount of data, demonstrating that CpG oligonucleotides worked in vitro and in vivo as described and supporting their therapeutic use. Thus, the full scope of the claims was enabled at the time the patent application was filed.

Accordingly, withdrawal of the rejection of claims 42-47, 49-54, 56-57, 82-85, 90, 92, 94, 96, 100 and 102-103 under 35 U.S.C. §112 is respectfully requested.

CONCLUSION

If the Examiner believes, after this Amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

Respectfully submitted,

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